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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/350,518	07/09/1999	JOHN C. REED	066654-0515	8259

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EXAMINER	
SANG, HONG	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
11/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SIP_Docket@mwe.com

Office Action Summary	Application No.	Applicant(s)	
	09/350,518	REED, JOHN C.	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,16,22-27,32-34,44,50-54,56,58-69,73-81 and 83-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,16,22-27,32-34,44,50-54,56,58-69,73-81 and 83-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Reed

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/2009 has been entered.

2. Claims 11, 12, 16, 22-27, 32-34, 44, 50-54, 56, 58-69, 73-81, and 83-109 are pending. Claims 1-10, 13-15, 17-21, 28-31, 35-43, 45-49, 55, 57, 70-72 and 82 have been cancelled. Claims 16, 25, 27, 34, 44, 67, 76, 78, 81 and 83 have been amended

3. Claims 11, 12, 16, 22-27, 32-34, 44, 50-54, 56, 58-69, 73-81, and 83-109 are under examination.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed on 10/15/2009 has been considered. A signed copy is attached hereto.

Rejections Withdrawn

5. The rejection of claims 11, 16, 22-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 73-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 under 35 U.S.C. 103(a) as being

unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print) in view of Takayama et al. (Cancer Res. 1998, 58: 3116-3131, IDS) is withdrawn upon further consideration and in view of new grounds of rejection.

Rejections Maintained

Claim Rejections - 35 USC § 102

6. The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 75-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 under 35 U.S.C. 102(b) as being anticipated by Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print) is maintained as evidenced by Krajewski et al. (Endocrine-Related Cancer, 1999, March, 6(1):29-40) and Exhibit 2 submitted by applicants on 7/23/2008

It is noted that the rejection of claims 22 and 73 is withdrawn upon further consideration. Moreover, claims 100, 102, 104, 106 and 108 are included in this rejection.

Argument A: The response states that independent claims 16, 25, 27, 34 and 44 have been amended to recite "in which the cancer is infiltrating [invasive] but has no lymph node involvement" and independent claims 67, 76, 78, 81 and 83 have been amended to recite "in which the cancer is infiltrating [invasive] but has spread no further than the lymph nodes local to breast". The response states that DCIS is confined to the ducts of the breast, whereas in stages I and II, breast cancer cells are invasive and have spread beyond the in situ stage and into the breast tissue.

Applicants' arguments have been carefully considered but are not persuasive. Turner et al. determined the expression of BAG-1 in benign breast epithelium (BBE), ductal carcinoma in situ (DCIS), and invasive carcinoma (IC) of the breast in 87 breast cancer patients (see abstract lines 3-5), of which 82 patients have IC and 5 patients have pure DCIS (see abstract lines 6-7). The IC studied by Turner is early stage, as evidence by Krajewski et al. Krajewski et al. disclose "Using a monoclonal antibody that we generated against BAG-1 protein and which recognizes all three of the known BAG-1 isoforms (Takayama et al. 1998), we examined the expression and in intracellular location of BAG-1 proteins in early-stage breast cancers (Turner et al. 1997)" (see page 36, column 1, paragraph 2). The Turner et al. 1997 mentioned by Krajewski et al. is the instant reference (see page 39 of Takayama, last reference). Early stage invasive carcinoma of breast includes stages I and II breast cancer, as evidenced by Exhibit 2 submitted by applicants on 7/23/2008 (see page 3). Exhibit 2 discloses that stage I breast cancer is defined as invasive breast cancer (cancer cells are breaking through to or invading neighboring normal tissue) in which the tumor measures up to two centimeters and no lymph nodes are involved, and stage II breast cancer is defined as invasive breast cancer in which the tumor measures at least two centimeters but not more than five centimeters, OR cancer has spread to the lymph nodes under the arm on the same side as the breast cancer. As such Turner et al. studied BAG-1 expression in breast cancer which is infiltrating [invasive] but has no lymph node involvement, and which is infiltrating [invasive] but has spread no further than the lymph nodes local to breast.

Argument B: The response states that while Turner disclosed that "10-year OS [overall survival] and DDFS [distant disease free survival] for patients with overexpression of cytoplasmic BAG- 1 in IC [invasive carcinoma] specimens was 75% and 70%, respectively, as compared with 62% and 35% for tumors with low cytoplasmic BAG-1 levels (p=0.06)," applicant discovered that 10-year OS and DMFS (distant metastasis-free survival) for patients with overexpression of BAG- 1 protein in stages I and II of breast cancer was 90% and 84%, respectively, as compared with 40% and 40% for those with low BAG-1 levels (p0.001) (see page 35 of the application as filed, lines 5-14, and Figure 1). This significant correlation of BAG-1 expression with 90% overall survival demonstrated by the large gap between the two survival rates and the small p-value is a result no ordinary person of skill in art could have predicted based on the teachings of Turner et al.

These arguments are not persuasive. While the results of the prior art are not identical to the applicant's, the method used by Turner is the same as instantly claimed. Moreover, although the patient population only includes stage 1 and stage 2 breast cancers, the change of the percentage of stage 1 or stage 2 in the population may affect the final results.

Claim Rejections - 35 USC § 103

7. The rejection of claims 11, 12, 16, 24-27, 32-34, 44, 50-54, 56, 58-61, 67-69, 75-81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997),

46(1): p69, print) in view of Sano et al. (US patent NO. 5665539) is maintained as evidenced by Krajewski et al. (Endocrine-Related Cancer, 1999, March, 6(1):29-40) and Exhibit 2 submitted by applicants on 7/23/2008.

It is noted that the rejection of claims 22 and 73 is withdrawn upon further consideration.

Applicant's presented same arguments as for 102(b) rejection and these arguments are not persuasive for the reasons set forth above.

8. The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-68, 75-79, 81, and 83-109 under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print) in view of Sauter et al. (British Journal of Cancer, 1997, 76(4): 494-501) is maintained as evidenced by Krajewski et al. (Endocrine-Related Cancer, 1999, March, 6(1):29-40) and Exhibit 2 submitted by applicants on 7/23/2008.

It is noted that the rejection of claims 22 and 73 is withdrawn upon further consideration.

Applicant's presented same arguments as for 102(b) rejection and these arguments are not persuasive for the reasons set forth above.

9. The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-68, 75-79, 81, and 83-109 under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print) in view of Love (US

Patent No. 6,221,622B1, Data of Patent 4/24/2001, earliest effective filing date 4/28/1998) is maintained as evidenced by Krajewski et al. (Endocrine-Related Cancer, 1999, March, 6(1):29-40) and Exhibit 2 submitted by applicants on 7/23/2008.

It is noted that the rejection of claims 22 and 73 is withdrawn upon further consideration.

Applicant's presented same arguments as for 102(b) rejection and these arguments are not persuasive for the reasons set forth above.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 11, 16, 22-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 73-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print), in view of Mather et al. (Clin. Cancer Res., 1998, Aug., 4:1851-1856), and McGuire et al. (US 5,188,964, Date of Patent: 2/23/1993), as evidenced by Krajewski et al. (Endocrine-Related Cancer, 1999, March, 6(1):29-40) and Exhibit 2 submitted by applicants on 7/23/2008.

The teaching of Turner et al. have been set forth above as they apply to claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 75-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 (see paragraph 6).

Turner et al. do not teach that the reference level of BAG-1 expression is determined by histogram, and determined relative to a level of BAG-1 expression produced by in vitro culture cells which produce BAG-1. However, these deficiencies are made up for in the teachings of Maher and McGuire.

Maher et al. disclose the use of immunohistochemistry, staining intensity and histogram analysis for evaluating the significance of CSF-1R expression on local recurrence in early stage breast cancer patients (see abstract and page 1854).

McGuire et al. teach a method of predicting disease-free survival in cancer patients by relating the number and amount of stress proteins in the cancer tissue to the probability of tumor recurrence (see abstract). McGuire et al. disclose that a relative measure of "overproduction" is used, and the units defining "overproduction" are relative to an arbitrarily assigned cancer cell line standard (the content of the same stress response proteins in a cell culture of human breast cancer cells) (see column 8, lines 62-65 and column 11, lines 20-25). McGuire et al. teach selection of the cutoff values is determined by statistical consideration and does not imply an absolute value (see column 9, lines 10-12).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use histogram analysis or in vitro cultured breast tumor cells to determine the reference level of BAG-1 in view of the teachings of Maher and

McGuire. One would have been motivated to do so with a reasonable expectation of success because the use of histogram analysis and in vitro cultured tumor cell line to determine the reference level (cutoff value) of a marker was well known in the prior art as shown by Maher and McGuire.

Claim Rejections - 35 USC § 103

12. Claims 11, 12, 16, 22-27, 32-34, 44, 50-54, 56, 58-69, 73-81, and 83-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (Breast Cancer Research and Treatment (Oct. 1997), 46(1): p69, print), in view of Mather et al. (Clin. Cancer Res., 1998, Aug., 4:1851-1856), McGuire et al. (US 5,188,964, Date of Patent: 2/23/1993), Sano et al. (US patent NO. 5665539), and Love (US Patent No. 6,221,622B1, Data of Patent 4/24/2001, earliest effective filing date 4/28/1998),

Turner et al. teach determining BAG-1 expression in benign breast epithelium (BBE), ductal carcinoma in situ (DCIS), and invasive carcinoma (IC) of the breast by immunohistochemistry using a monoclonal antibody on 87 cases containing IC or pure CDIS and BBE, wherein the patients had a median follow-up of 13 years. Turner et al. teach that the slides were rated on a scale of intensity and % distribution within the BBE, DCIS and IC components. Turner et al. teach that there is a statistic significant over expression of nuclear and cytoplasmic BAG1 in cancer patients compared to BBE patients. Turner et al. teach that the 10-year overall survival (OS) and distant disease free survival (DDFS) for breast cancer patients with overexpression of BAG-I in IC specimens was 75% and 70%, respectively, compared to 62% and 35% for tumors with

low cytoplasmic BAG-I levels. Therefore, Turner et al. teach the method of correlating the disease-free or overall survival of an individual having a breast cancer tumor with the overexpression of BAG-1 protein. Turner et al. conclude that the subcellular location of BAG-1 may have prognostic importance with respect to survival of breast cancer patients. The instant specification teaches that the reference level may be determined by measuring level of expression of BAG in non-tumorous cancer cells from the same tissue as the tissue of cancer cells to be tested (see specification page 18, lines 4-13), the reference level may also be determined by comparison of BAG expression levels in populations of patients having the same cancer (see specification page 18, lines 24-26), and the reference level can also represent the level of BAG protein in one or more compartments of the cell (see specification page 21, lines 3-5). Turner et al. teach that breast cancer patients having overexpression of BAG-1 in either nucleus or cytoplasm have higher rate of 10-year survival and distant disease free survival compared to patients having low expression of nuclear or cytoplasmic BAG-I. Therefore, Turner teaches comparing to a reference level.

Turner et al. do not expressly disclose that the invasive carcinoma of breast cancer include stage I and/or stage II cancer. Turner et al. do not teach that the reference level of BAG-1 expression is determined by histogram, and determined relative to a level of BAG-1 expression produced by in vitro culture cells which produce BAG-1. Turner et al. do not teach the immuno-polymerase chain reaction (immuno-PCR) assay, and measuring the level of BAG-1 protein in a sample of body fluid

containing breast cancer cells. However, these deficiencies are made up for in the teachings of Maher, McGuire, Sano and Love.

Maher et al. teach using immunohistochemistry, staining intensity and histogram analysis for evaluating the significance of CSF-1R expression on local recurrence in early stage (stages I and II) breast cancer patients (see abstract, Table 1, page 1854). Maher et al. disclose that identification of risk factors for local recurrence in the conservatively treated breast cancer (i.e. early stage breast cancer) patients remains an active area of clinical investigation (see page 1854, column 2).

McGuire et al. teach a method of predicting disease-free survival in breast cancer patients (stages I and II) by relating the number and amount of stress proteins in the cancer tissue to the probability of tumor recurrence (see abstract and Table 3A). McGuire et al. teach that there is a great need for a general method of predicting tumor recurrence in breast cancer patients which has not progressed to the axillarly lymph nodes (node-negative breast cancers) or in cancer patients once the primary tumor is detected (see column 7, lines 23-26). McGuire et al. disclose that a relative measure of “overproduction” is used, and the units defining ”overproduction” are relative to an arbitrarily assigned cancer cell line standard (the content of the same stress response proteins in a cell culture of human breast cancer cells) (see column 8, lines 62-65 and column 11, lines 20-25). McGuire et al. teach selection of the cutoff values is determined by statistical consideration and does not imply an absolute value (see column 9, lines 10-12). McGuire et al. teach using histograms for determination of the cutoff values (see Examples 2 and 3, and Figure 2).

Sano et al. teach detection of a protein using immuno-PCR (see abstract).

Love teaches a method of obtaining fluids, marker substances and cellular material from single milk ducts in the breasts of a patient for cancer diagnosis (see column 3, lines 5-20), wherein the cellular material comprises epithelial cells from the lining of the duct, and the epithelial and other cells obtained by the method can be morphologically, histochemically, and/or immmunohistochemically examined to determine if they are abnormal and to assess the likelihood of a cancer or pre\-cancerous condition present in the cellular lining of the duct (see column 3, lines 35-45).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method of Turner for predicting the disease-free or overall survival of early stage (stages I and/or II) breast cancer patients. One would have been motivated to do so because both Maher and McGuire et al. teach that there is a great need for a general method of predicting tumor recurrence in early stage breast cancer patients, and Turner et al. conclude that the subcellular location of BAG-1 may have prognostic importance with respect to survival of breast cancer patients. One would have had a reasonable expectation of success because Turner et al. have shown that the 10-year overall survival (OS) and distant disease free survival (DDFS) for breast cancer patients with overexpression of BAG-I in IC specimens was 75% and 70%, respectively, compared to 62% and 35% for tumors with low cytoplasmic BAG-I levels.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use histogram analysis or in vitro cultured breast tumor

cells to determine the reference level of BAG-1 in view of the teachings of Maher and McGuire. One would have been motivated to do so with a reasonable expectation of success because the use of histogram analysis and in vitro cultured tumor cell line to determine the reference level (cutoff value) of a marker was well known in the prior art as shown by Maher and McGuire.

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the methods of Turner et al. and the detection techniques of Sano et al. and one would have been motivated to do so because the detection techniques of Sano are useful and efficient methods for detection of a protein. Moreover, one of ordinary skill in the art would have a reasonable expectation of success of detecting BAG-1 using immuno-PCR because immuno-PCR was a well-established method for protein detection at the time the invention was made.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Turner et al. to detect BAG-1 in ductal fluid instead of in tissue sample for cancer prognosis in view of the teachings of Love. One would have been motivated to do so because unlike detecting BAG-1 in tissue sample where the tumor must be first identified by other methods such as imaging, and biopsy must be performed, detecting BAG-1 in ductal fluid is non-invasive and it provides early cancer detection without the need of imaging the tumor before collecting the fluid. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to do so because Love teaches how to obtain cellular material

from milk duct for breast cancer diagnosis and Turner teaches a method of prognosis of breast cancer by detecting BAG-1 protein in breast tumor cells.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643